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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/808,846	03/24/2004	Erwin Gelfand	5802-1-1	6711
22442	7590	11/21/2007		
SHERIDAN ROSS PC 1560 BROADWAY SUITE 1200 DENVER, CO 80202			EXAMINER ROONEY, NORA MAUREEN	
			ART UNIT 1644	PAPER NUMBER
			MAIL DATE 11/21/2007	DELIVERY MODE PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/808,846	Applicant(s) GELFAND ET AL.	
	Examiner Nora M. Rooney	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 September 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 36-53 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 36-53 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Claims 36-53 are pending.
2. Claims 36-53 are currently under examination as they read on a method for reducing airway hyperresponsiveness by administering a phosphoantigen to a mammal.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 36-53 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *This is a New Matter rejection for the following reasons:*

The method to reduce airway hyperresponsiveness in a mammal, comprising increasing gamma delta T cell action in a mammal that has, or is at risk of developing, a respiratory condition associated with airway hyperresponsiveness by administering a phosphoantigen to said mammal, wherein administration of said phosphoantigen reduces airway hyperresponsiveness in said mammal of claim 36; wherein the phosphoantigen comprises isoprenylpyrophosphate (IPP)

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of claim 37; wherein said pyrophosphate is administered so that gamma delta T cells in the lung tissue of said mammal increases of claim 38; wherein said phosphoantigen is administered so that gamma delta T cells in said mammal are activated of claim 39; wherein said phosphoantigen is targeted to gamma delta T cells in the lung tissue of said mammal of claim 40; wherein said phosphoantigen is targeted to gamma delta T cells having T cell receptor selected from the group consisting of a murine TCR comprising Vgamma4 and a human TCR comprising Vgamma1 of claim 41; wherein said phosphoantigen is administered by a route selected from the group consisting of inhaled, intratracheal and nasal routes of claim 42; wherein said phosphoantigen is administered to said mammal in an amount effecting to reduce airway hyperresponsiveness in said mammal as compared to prior to administration of said phosphoantigen of claim 43; wherein said phosphoantigen is administered with a pharmaceutically acceptable excipient of claim 44; wherein said phosphoantigen is administered within between 1 hour and 6 days of an initial diagnosis of airway hyperresponsiveness in said mammal of claim 45; wherein said phosphoantigen is administered within less than about 72 hours of an initial diagnosis of airway hyperresponsiveness in said mammal of claim 46; wherein said phosphoantigen is administered prior to development of airway hyperresponsiveness in said mammal; wherein increasing gamma delta T cell action by administration of said phosphoantigen decreases airway methacholine responsiveness in said mammal of claim 48; wherein increasing gamma delta T cell action by administration of said phosphoantigen reduces airway hyperresponsiveness of said mammal such that the FEV1 value of said mammal is improved by at least about 5% of claim 49; wherein increasing gamma delta T cell action by administration of said phosphoantigen improves said mammal's PC_{20methacholine} FEVt value obtained before increasing gamma delta T cell action when

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the mammal is provoked with a first concentration of methacholine is substantially the same as the $PC_{20\text{methacholine}}$ FEVt value obtained after increasing gamma delta T cell action when the mammal is provoked with double the amount of the first concentration of methacholine of claim 50; wherein said first concentration of methacholine is between about 0.01 mg/ml and about 8 mg/ml; wherein said airway hyperresponsiveness is associated with a disease selected from the group consisting of chronic obstructive disease of the airways and asthma **represents a departure from the specification and the claims as originally filed** for the same reasons as set forth in the Office Action mailed on 05/03/2007.

Applicant's arguments submitted on 09/04/2007 have been fully considered, but are not found persuasive.

Applicant argues that

"Applicants specifically traverse the Examiner's assertion that the specification does not contemplate using any phosphoantigen in the presently claimed method. Page 31, lines 21-24 state the following: "For the activation of $\gamma\delta$ T cells, the present invention also includes the use of 'phospho-antigens'. Phospho-antigens are antigens containing phosphate groups such as isoprenylpyrophosphate (IPP) and many others that have been characterized by the research groups of Michael Brenner and others (e.g., Tanaka et al., 1995, *Nature* 375:155- 158)." Therefore, the specification clearly teaches the use of phosphoantigens (spelled "phospho-antigen" in the specification) for use in activation of $\gamma\delta$ T cells, and provides a reference to the knowledge of such phosphoantigens in the art. The Examiner asserts that the specification is devoid of a teaching to use phosphoantigens in the claimed method, but this is not accurate. To the contrary, a careful reading of the specification reveals that this paragraph is one in a series of paragraphs beginning on page 25, line 5, and ending on page 33, line 10, which describe a variety of agents that can be used to act on $\gamma\delta$ T cells and increase the proliferation, activation/biological activity and/or survival of $\gamma\delta$ T cells in the lung tissue of an animal, and/or the recruitment of other regulatory $\gamma\delta$ T cells to the lung tissue of the animal, such that airway hyperresponsiveness is reduced in the animal (emphasis added). Indeed, referring to page 25, lines 5-20, the specification teaches: "In one embodiment, the

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method of the present invention includes the use of a variety of agents (i.e., regulatory compounds) which, by acting on $\gamma\delta$ T cells, increase the proliferation, activation/biological activity, and/or survival of $\gamma\delta$ T cells in the lung tissue of an animal, and/or the recruitment of other regulatory $\gamma\delta$ T cells to the lung tissue of the animal, such that airway hyperresponsiveness is reduced in the animal. Such agents are generally referred to herein as $\gamma\delta$ T cells agonists. According to the present invention, a $\gamma\delta$ T cell agonist is any agent which increases, typically by direct action on the cell, the proliferation, activation/biological activity, and/or survival of $\gamma\delta$ T cells, and includes agents which act directly on the $\gamma\delta$ T cell receptor. A $\gamma\delta$ T cell agonist, as referred to herein, can further include, for example, compounds that are products of rational drug design, natural products, and compounds having partially or fully defined $\gamma\delta$ T cell stimulatory properties. A $\gamma\delta$ T cell agonist can be a protein-based compound, a carbohydrate-based compound, a lipid-based compound, a nucleic acid-based compound, a natural organic compound, a synthetically derived organic compound, an antibody, or fragments thereof. A variety of known $\gamma\delta$ T cell agonists are described below and all are encompassed by the present invention." The specification then goes on to list a variety of agents that can be used in the method of the invention, paragraph by paragraph, which includes the paragraph on page 31 and the reference to phosphoantigens, clearly identifying this agent as useful in the method of the invention. Accordingly, it is completely incorrect to state that the specification never contemplated using phosphoantigens in the claimed method.

If the Examiner is objecting to the use of the spelling "phospho-antigen" instead of "phosphoantigen", this is a mere difference in the spelling of the term. However, given the clear definition in the specification of "antigens containing phosphate groups such as isoprenylpyrophosphate (IPP) and many others that have been characterized by the research groups of Michael Brenner and others (e.g., Tanaka et al., 1995, *Nature* 375:155-158)", as discussed above, it is clear to one of skill in the art that these are alternate spellings of the same word. However, in order to alleviate this portion of the Examiner's concerns regarding this term, the specification has been amended to remove the hyphen in the word "phosphoantigen" so that it is more consistent with the spelling used in the literature. Given that the specification provides a definition and reference to a publication clearly establishing the identity of the term, this amendment adds no new matter. Mere rephrasing of a passage does not constitute new matter. Accordingly, a rewording of a passage where the same meaning remains intact is permissible. *In re Anderson*, 471 F.2d 1237, 176 USPQ 331 (CCPA 1973). The mere inclusion of dictionary or art recognized definitions known at the time of filing an application would not be considered new matter. An amendment to correct an obvious error does not constitute new matter where one skilled in the art would not only recognize the existence of error in the specification, but also the appropriate correction. *In re Odd*, 443 F.2d 1200, 170 USPQ 268 (CCPA 1971). "

It is the Examiner's position that the recited method does not have clear support in the specification, contrary to Applicant's assertion. The specification is directed to a method of identifying compounds that regulate airway hyperresponsiveness by modulating T cell action. The specification is not directed to a method of reducing airway hyperresponsiveness using a phosphoantigen. Though the specification mentions phospho-antigen and IPP as possible compounds that can be identified in the disclosed method, the specification does not provide clear support for a method of using the phospho-antigen or IPP compounds.

5. Claims 36-53 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of : a method to reduce airway hyperresponsiveness in a mammal, consisting essentially of increasing gamma delta T cell action in a mammal that has, or is at risk of developing, a respiratory condition associated with airway hyperresponsiveness by administering TNF-alpha to the lung tissue of said mammal wherein administration of said TNF-alpha reduces airway hyperresponsiveness in said mammal; wherein said TNF-alpha is administered so that gamma delta T cells in the lung tissue of said mammal increases; wherein said TNF-alpha is administered so that gamma delta T cells in said mammal are activated; wherein said TNF-alpha is targeted to gamma delta T cells in the lung tissue of said mammal; wherein said TNF-alpha is targeted to gamma delta T cells having T cell receptor selected from

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the group consisting of a murine TCR comprising Vgamma4 and a human TCR comprising Vgamma1; wherein said TNF-alpha is administered by a route selected from the group consisting of inhaled, intratracheal and nasal routes; wherein said TNF-alpha is administered to said mammal in an amount effective to reduce airway hyperresponsiveness in said mammal as compared to prior to administration of said TNF-alpha; wherein said TNF-alpha is administered with a pharmaceutically acceptable excipient; wherein said TNF-alpha is administered within between 1 hour and 6 days of an initial diagnosis of airway hyperresponsiveness in said mammal; wherein said TNF-alpha is administered within less than about 72 hours of an initial diagnosis of airway hyperresponsiveness in said mammal; wherein said TNF-alpha is administered prior to development of airway hyperresponsiveness in said mammal; wherein increasing gamma delta T cell action by administration of said TNF-alpha decreases airway methacholine responsiveness in said mammal; wherein increasing gamma delta T cell action by administration of said TNF-alpha reduces airway hyperresponsiveness of said mammal such that the FEV1 value of said mammal is improved by at least about 5%; wherein increasing gamma delta T cell action by administration of said TNF-alpha improves said mammal's PC_{20methacholine} FEVt value obtained before increasing gamma delta T cell action when the mammal is provoked with a first concentration of methacholine is substantially the same as the PC_{20methacholine} FEVt value obtained after increasing gamma delta T cell action when the mammal is provoked with double the amount of the first concentration of methacholine; wherein said first concentration of methacholine is between about 0.01 mg/ml and about 8 mg/ml; wherein said airway hyperresponsiveness is associated with a disease selected from the group consisting of chronic obstructive disease of the airways and asthma.

Applicant is not in possession of : a method to reduce airway hyperresponsiveness in a mammal, comprising increasing gamma delta T cell action in a mammal that has, or is at risk of developing, a respiratory condition associated with airway hyperresponsiveness by administering **a phosphoantigen** to said mammal, wherein administration of said **phosphoantigen** reduces airway hyperresponsiveness in said mammal of claim 36; wherein the **phosphoantigen** comprises **isoprenylpyrophosphate (IPP)** of claim 37; wherein said **pyrophosphate** is administered so that gamma delta T cells in the lung tissue of said mammal increases of claim 38; wherein said **phosphoantigen** is administered so that gamma delta T cells in said mammal are activated of claim 39; wherein said **phosphoantigen** is targeted to gamma delta T cells in the lung tissue of said mammal of claim 40; wherein said **phosphoantigen** is targeted to gamma delta T cells having T cell receptor selected from the group consisting of a murine TCR comprising Vgamma4 and a human TCR comprising Vgamma1 of claim 41; wherein said **phosphoantigen** is administered by a route selected from the group consisting of inhaled, intratracheal and nasal routes of claim 42; wherein said **phosphoantigen** is administered to said mammal in an amount effecting to reduce airway hyperresponsiveness in said mammal as compared to prior to administration of said phosphoantigen of claim 43; wherein said **phosphoantigen** is administered with a pharmaceutically acceptable excipient of claim 44; wherein said **phosphoantigen** is administered within between 1 hour and 6 days of an initial diagnosis of airway hyperresponsiveness in said mammal of claim 45; wherein said **phosphoantigen** is administered within less than about 72 hours of an initial diagnosis of airway hyperresponsiveness in said mammal of claim 46; wherein said **phosphoantigen** is administered

prior to development of airway hyperresponsiveness in said mammal; wherein increasing gamma delta T cell action by administration of said **phosphoantigen** decreases airway methacholine responsiveness in said mammal of claim 48; wherein increasing gamma delta T cell action by administration of said **phosphoantigen** reduces airway hyperresponsiveness of said mammal such that the FEV1 value of said mammal is improved by at least about 5% of claim 49; wherein increasing gamma delta T cell action by administration of said **phosphoantigen** improves said mammal's PC_{20methacholine} FEVt value obtained before increasing gamma delta T cell action when the mammal is provoked with a first concentration of methacholine is substantially the same as the PC_{20methacholine} FEVt value obtained after increasing gamma delta T cell action when the mammal is provoked with double the amount of the first concentration of methacholine of claim 50; wherein said first concentration of methacholine is between about 0.01 mg/ml and about 8 mg/ml; wherein said airway hyperresponsiveness is associated with a disease selected from the group consisting of chronic obstructive disease of the airways and asthma for the same reasons as set forth in the Office Action mailed on 05/03/2007.

Applicant's arguments filed on 09/04/2007 have been fully considered, but are not found persuasive.

Applicant argues that the specification teaches that:

"For the activation of $\gamma\delta$ T cells, the present invention also includes the use of 'phospho-antigens'. Phospho-antigens are antigens containing phosphate groups such as isoprenylpyrophosphate (IPP) and many others that have been characterized by the research groups of Michael Brenner and others (e.g., Tanaka et al., 1995, *Nature* 375:155-158)" (Page 31, lines 21-24). Therefore, the specification clearly teaches the use of phosphoantigens (spelled "phospho-antigen" in the specification, which is simply an alternate spelling for the term, as discussed above) for use in activation of $\gamma\delta$ T cells, and

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provides a reference to the knowledge of such phosphoantigens in the art. To attempt to obviate the Examiner's concerns, as discussed above, the specification has been amended to remove the hyphen in the word "phosphoantigen" so that it is more consistent with the spelling used in the literature. Given that the specification provides a definition and reference to a publication clearly establishing the identity of the term, this amendment adds no new matter.

Moreover, the term "phosphoantigens" was well-known to those of skill in the art at the time of the invention. As evidence of this position, enclosed herewith are two publications (Belmant et al., 2000, *FASEB* 17:1669-1670; and Espinosa et al., 2001, *Microbes and Infection* 3:645-654), both of which establish that the term "phosphoantigen" was well-known in the art at the time of the invention, and that multiple examples of natural and synthetic phosphoantigens were known. These references also further establish that at the time of the invention, it was known that phosphoantigens could activate $\gamma\delta$ T cells. Accordingly, the art already recognizes the structural features common to the genus of phosphoantigens and therefore, the skilled artisan does not need to "figure out what a phosphoantigen looks like". One of skill in the art is already apprised of what is a phosphoantigen, including different examples of members of the genus, and accordingly, one of skill in the art can readily envision multiple contemplated phosphoantigen possibilities recited in the instant claims. Establishment of sufficient written description does not require that Applicants describe each and every embodiment that may fall within the scope of the claims. The analysis of whether the specification complies with the written description requirement should be conducted from the standpoint of one of skill in the art at the time the application was filed (see, e.g., *Wang Labs. v. Toshiba Corp.*, 993 F.2d 858, 865, 26 USPQ2d 1767, 1774 (Fed. Cir. 1993)) and should include a determination of the field of the invention and the level of skill and knowledge in the art. Information which is well known in the art need not be described in detail in the specification. See, e.g., *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379-80, 231 USPQ 81, 90 (Fed. Cir. 1986) (emphasis added). See also MPEP 2163II(A)(2). Applicants submit that the specification description is sufficient to place the inventors in possession of the claimed invention at the time of filing.

With regard to the Examiner's concern that throughout the literature "IPP" stands for a different molecule, namely isopentenylpyrophosphate, it is agreed that in the literature, isopentenylpyrophosphate is also denoted by the acronym, IPP. However, it is noted that isopentenylpyrophosphate is in fact a particular compound included in the larger family of isoprenylpyrophosphates. "Isoprenyl" is a more generic term than "isopentenyl", and in fact "prenyl" stands for a skeleton of 5n carbon atoms; however, this carbon skeleton can undergo various substitutions resulting in many different products (alcohol moiety, acid moiety, different alkyl substitutions, etc...). When n=1, then isoprenyl is isopentenyl (C5, n=1), but larger isoprenyls exist (e.g., geranyl (C10, n=2), farnesyl (C15, n=3), geranylgeranyl (C20, n=4)). Therefore, one

isoprenylpyrophosphate that can be used in the present invention would be isopentenylpyrophosphate. "

It is the Examiner's position that the specification has not adequately described a correlation between function (reduces airway hyperresponsiveness) and structure responsible for reducing airway hyperresponsiveness such that one of ordinary skill in the art would have known which phosphoantigens could be used to generate the disclosed function of reducing airway hyperresponsiveness in a mammal. Possession may not be shown by merely describing how to obtain possession of members of the claimed genus or how to identify their common structural features. See *University of Rochester*, 358 F.3d at 927, 69 USPQ2d at 1895. "Without a correlation between structure and function, the claims do little more than define the claimed invention by function. That is not sufficient to satisfy the written description requirement." *Ex parte Kubin*, 83 U.S.P.Q.2d 1410 (BPAI 2007). The specification does not adequately describe the genus of all phosphoantigen non-peptide compounds for use in the claimed invention.

Contrary to Applicant's assertion one of ordinary skill in the art would not be able to determine which phosphoantigens would work in the claimed invention since neither the exemplary embodiments nor the specification's general method appears to describe structural features, in structural terms, that are common to the genus of phosphoantigens that would work to reduce airway hyperresponsiveness in the claimed invention. Applicant's assertion that all phosphoantigens would work is not supported by examples or description in the specification. Further, the art shows that "both the number and position of the phosphate groups, as well as the residues connected with the carbon backbone are required for stimulation" of $\gamma\delta$ T cells. (In

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particular, Burk et al., PTO-892, Reference U, abstract, whole document). No such structure requisite structure has been described in the specification.

6. No claim is allowed.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nora M. Rooney whose telephone number is (571) 272-9937. The examiner can normally be reached Monday through Friday from 8:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571)

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272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

November 13, 2007

Nora M. Rooney, M.S., J.D.

Patent Examiner

Technology Center 1600

DETAILED ACTION

1. Claims 36-53 are pending.
2. Claims 36-53 are currently under examination as they read on a method for reducing airway hyperresponsiveness by administering a phosphoantigen to a mammal.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 36-53 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *This is a New Matter rejection for the following reasons:*

The method to reduce airway hyperresponsiveness in a mammal, comprising increasing gamma delta T cell action in a mammal that has, or is at risk of developing, a respiratory condition associated with airway hyperresponsiveness by administering a phosphoantigen to said mammal, wherein administration of said phosphoantigen reduces airway hyperresponsiveness in said mammal of claim 36; wherein the phosphoantigen comprises isoprenylpyrophosphate (IPP)

of claim 37; wherein said pyrophosphate is administered so that gamma delta T cells in the lung tissue of said mammal increases of claim 38; wherein said phosphoantigen is administered so that gamma delta T cells in said mammal are activated of claim 39; wherein said phosphoantigen is targeted to gamma delta T cells in the lung tissue of said mammal of claim 40; wherein said phosphoantigen is targeted to gamma delta T cells having T cell receptor selected from the group consisting of a murine TCR comprising Vgamma4 and a human TCR comprising Vgamma1 of claim 41; wherein said phosphoantigen is administered by a route selected from the group consisting of inhaled, intratracheal and nasal routes of claim 42; wherein said phosphoantigen is administered to said mammal in an amount effecting to reduce airway hyperresponsiveness in said mammal as compared to prior to administration of said phosphoantigen of claim 43; wherein said phosphoantigen is administered with a pharmaceutically acceptable excipient of claim 44; wherein said phosphoantigen is administered within between 1 hour and 6 days of an initial diagnosis of airway hyperresponsiveness in said mammal of claim 45; wherein said phosphoantigen is administered within less than about 72 hours of an initial diagnosis of airway hyperresponsiveness in said mammal of claim 46; wherein said phosphoantigen is administered prior to development of airway hyperresponsiveness in said mammal; wherein increasing gamma delta T cell action by administration of said phosphoantigen decreases airway methacholine responsiveness in said mammal of claim 48; wherein increasing gamma delta T cell action by administration of said phosphoantigen reduces airway hyperresponsiveness of said mammal such that the FEV1 value of said mammal is improved by at least about 5% of claim 49; wherein increasing gamma delta T cell action by administration of said phosphoantigen improves said mammal's PC_{20methacholine} FEVt value obtained before increasing gamma delta T cell action when

the mammal is provoked with a first concentration of methacholine is substantially the same as the $PC_{20\text{methacholine}}$ FEVt value obtained after increasing gamma delta T cell action when the mammal is provoked with double the amount of the first concentration of methacholine of claim 50; wherein said first concentration of methacholine is between about 0.01 mg/ml and about 8 mg/ml; wherein said airway hyperresponsiveness is associated with a disease selected from the group consisting of chronic obstructive disease of the airways and asthma **represents a departure from the specification and the claims as originally filed** for the same reasons as set forth in the Office Action mailed on 05/03/2007.

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"Applicants specifically traverse the Examiner's assertion that the specification does not contemplate using any phosphoantigen in the presently claimed method. Page 31, lines 21-24 state the following: "For the activation of $\gamma\delta$ T cells, the present invention also includes the use of 'phospho-antigens'. Phospho-antigens are antigens containing phosphate groups such as isoprenylpyrophosphate (IPP) and many others that have been characterized by the research groups of Michael Brenner and others (e.g., Tanaka et al., 1995, *Nature* 375:155- 158)." Therefore, the specification clearly teaches the use of phosphoantigens (spelled "phospho-antigen" in the specification) for use in activation of $\gamma\delta$ T cells, and provides a reference to the knowledge of such phosphoantigens in the art. The Examiner asserts that the specification is devoid of a teaching to use phosphoantigens in the claimed method, but this is not accurate. To the contrary, a careful reading of the specification reveals that this paragraph is one in a series of paragraphs beginning on page 25, line 5, and ending on page 33, line 10, which describe a variety of agents that can be used to act on $\gamma\delta$ T cells and increase the proliferation, activation/biological activity and/or survival of $\gamma\delta$ T cells in the lung tissue of an animal, and/or the recruitment of other regulatory $\gamma\delta$ T cells to the lung tissue of the animal, such that airway hyperresponsiveness is reduced in the animal (emphasis added). Indeed, referring to page 25, lines 5-20, the specification teaches: "In one embodiment, the

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method of the present invention includes the use of a variety of agents (i.e., regulatory compounds) which, by acting on $\gamma\delta$ T cells, increase the proliferation, activation/biological activity, and/or survival of $\gamma\delta$ T cells in the lung tissue of an animal, and/or the recruitment of other regulatory $\gamma\delta$ T cells to the lung tissue of the animal, such that airway hyperresponsiveness is reduced in the animal. Such agents are generally referred to herein as $\gamma\delta$ T cells agonists. According to the present invention, a $\gamma\delta$ T cell agonist is any agent which increases, typically by direct action on the cell, the proliferation, activation/biological activity, and/or survival of $\gamma\delta$ T cells, and includes agents which act directly on the $\gamma\delta$ T cell receptor. A $\gamma\delta$ T cell agonist, as referred to herein, can further include, for example, compounds that are products of rational drug design, natural products, and compounds having partially or fully defined $\gamma\delta$ T cell stimulatory properties. A $\gamma\delta$ T cell agonist can be a protein-based compound, a carbohydrate-based compound, a lipid-based compound, a nucleic acid-based compound, a natural organic compound, a synthetically derived organic compound, an antibody, or fragments thereof. A variety of known $\gamma\delta$ T cell agonists are described below and all are encompassed by the present invention." The specification then goes on to list a variety of agents that can be used in the method of the invention, paragraph by paragraph, which includes the paragraph on page 31 and the reference to phosphoantigens, clearly identifying this agent as useful in the method of the invention. Accordingly, it is completely incorrect to state that the specification never contemplated using phosphoantigens in the claimed method.

If the Examiner is objecting to the use of the spelling "phospho-antigen" instead of "phosphoantigen", this is a mere difference in the spelling of the term. However, given the clear definition in the specification of "antigens containing phosphate groups such as isoprenylpyrophosphate (IPP) and many others that have been characterized by the research groups of Michael Brenner and others (e.g., Tanaka et al., 1995, *Nature* 375:155-158)", as discussed above, it is clear to one of skill in the art that these are alternate spellings of the same word. However, in order to alleviate this portion of the Examiner's concerns regarding this term, the specification has been amended to remove the hyphen in the word "phosphoantigen" so that it is more consistent with the spelling used in the literature. Given that the specification provides a definition and reference to a publication clearly establishing the identity of the term, this amendment adds no new matter. Mere rephrasing of a passage does not constitute new matter. Accordingly, a rewording of a passage where the same meaning remains intact is permissible. *In re Anderson*, 471 F.2d 1237, 176 USPQ 331 (CCPA 1973). The mere inclusion of dictionary or art recognized definitions known at the time of filing an application would not be considered new matter. An amendment to correct an obvious error does not constitute new matter where one skilled in the art would not only recognize the existence of error in the specification, but also the appropriate correction. *In re Odd*, 443 F.2d 1200, 170 USPQ 268 (CCPA 1971). "

It is the Examiner's position that the recited method does not have clear support in the specification, contrary to Applicant's assertion. The specification is directed to a method of identifying compounds that regulate airway hyperresponsiveness by modulating T cell action. The specification is not directed to a method of reducing airway hyperresponsiveness using a phosphoantigen. Though the specification mentions phospho-antigen and IPP as possible compounds that can be identified in the disclosed method, the specification does not provide clear support for a method of using the phospho-antigen or IPP compounds.

5. Claims 36-53 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for : a method to reduce airway hyperresponsiveness in a mammal, consisting essentially of increasing gamma delta T cell action in a mammal that has, or is at risk of developing, a respiratory condition associated with airway hyperresponsiveness by administering TNF-alpha to the lung tissue of said mammal wherein administration of said TNF-alpha reduces airway hyperresponsiveness in said mammal; wherein said TNF-alpha is administered so that gamma delta T cells in the lung tissue of said mammal increases; wherein said TNF-alpha is administered so that gamma delta T cells in said mammal are activated; wherein said TNF-alpha is targeted to gamma delta T cells in the lung tissue of said mammal; wherein said TNF-alpha is targeted to gamma delta T cells having T cell receptor selected from the group consisting of a murine TCR comprising Vgamma4 and a human TCR comprising Vgamma1; wherein said TNF-alpha is administered by a route selected from the group consisting of inhaled, intratracheal and nasal routes; wherein said TNF-alpha is administered to said mammal in an amount effective to reduce airway hyperresponsiveness in said mammal as

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compared to prior to administration of said TNF-alpha; wherein said TNF-alpha is administered with a pharmaceutically acceptable excipient; wherein said TNF-alpha is administered within between 1 hour and 6 days of an initial diagnosis of airway hyperresponsiveness in said mammal; wherein said TNF-alpha is administered within less than about 72 hours of an initial diagnosis of airway hyperresponsiveness in said mammal; wherein said TNF-alpha is administered prior to development of airway hyperresponsiveness in said mammal; wherein increasing gamma delta T cell action by administration of said TNF-alpha decreases airway methacholine responsiveness in said mammal; wherein increasing gamma delta T cell action by administration of said TNF-alpha reduces airway hyperresponsiveness of said mammal such that the FEV1 value of said mammal is improved by at least about 5%; wherein increasing gamma delta T cell action by administration of said TNF-alpha improves said mammal's PC_{20methacholine} FEVt value obtained before increasing gamma delta T cell action when the mammal is provoked with a first concentration of methacholine is substantially the same as the PC_{20methacholine} FEVt value obtained after increasing gamma delta T cell action when the mammal is provoked with double the amount of the first concentration of methacholine; wherein said first concentration of methacholine is between about 0.01 mg/ml and about 8 mg/ml; wherein said airway hyperresponsiveness is associated with a disease selected from the group consisting of chronic obstructive disease of the airways and asthma; does not reasonably provide enablement for a method to reduce airway hyperresponsiveness in a mammal, comprising increasing gamma delta T cell action in a mammal that has, or is at risk of developing, a respiratory condition associated with airway hyperresponsiveness by administering a **phosphoantigen** to said mammal, wherein administration of said **phosphoantigen** reduces airway hyperresponsiveness in said mammal of

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claim 36; wherein the **phosphoantigen** comprises **isoprenylpyrophosphate (IPP)** of claim 37; wherein said **pyrophosphate** is administered so that gamma delta T cells in the lung tissue of said mammal increases of claim 38; wherein said **phosphoantigen** is administered so that gamma delta T cells in said mammal are activated of claim 39; wherein said **phosphoantigen** is targeted to gamma delta T cells in the lung tissue of said mammal of claim 40; wherein said **phosphoantigen** is targeted to gamma delta T cells having T cell receptor selected from the group consisting of a murine TCR comprising Vgamma4 and a human TCR comprising Vgamma1 of claim 41; wherein said **phosphoantigen** is administered by a route selected from the group consisting of inhaled, intratracheal and nasal routes of claim 42; wherein said **phosphoantigen** is administered to said mammal in an amount effecting to reduce airway hyperresponsiveness in said mammal as compared to prior to administration of said phosphoantigen of claim 43; wherein said **phosphoantigen** is administered with a pharmaceutically acceptable excipient of claim 44; wherein said **phosphoantigen** is administered within between 1 hour and 6 days of an initial diagnosis of airway hyperresponsiveness in said mammal of claim 45; wherein said **phosphoantigen** is administered within less than about 72 hours of an initial diagnosis of airway hyperresponsiveness in said mammal of claim 46; wherein said **phosphoantigen** is administered prior to development of airway hyperresponsiveness in said mammal; wherein increasing gamma delta T cell action by administration of said **phosphoantigen** decreases airway methacholine responsiveness in said mammal of claim 48; wherein increasing gamma delta T cell action by administration of said **phosphoantigen** reduces airway hyperresponsiveness of said mammal such that the FEV1 value of said mammal is improved by at least about 5% of claim 49; wherein increasing gamma delta T

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cell action by administration of said **phosphoantigen** improves said mammal's $PC_{20\text{methacholine}}$ FEVt value obtained before increasing gamma delta T cell action when the mammal is provoked with a first concentration of methacholine is substantially the same as the $PC_{20\text{methacholine}}$ FEVt value obtained after increasing gamma delta T cell action when the mammal is provoked with double the amount of the first concentration of methacholine of claim 50; wherein said first concentration of methacholine is between about 0.01 mg/ml and about 8 mg/ml; wherein said airway hyperresponsiveness is associated with a disease selected from the group consisting of chronic obstructive disease of the airways and asthma. The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation for the same reasons as set forth in the Office Action mailed on 05/03/2007.

Applicant's arguments and declaration submitted on 09/04/2007 have been fully considered, but are insufficient to overcome the enablement rejection.

Applicant argues that:

"Applicants submit that the Examiner is incorrect in making the statement that the claimed method "would not work". This is not at all supported by the specification, the knowledge in the art at the time of the invention, or the evidence of record. First, Applicants submit that it was known in the art at the time of the invention that phosphoantigens are a class of agents that can activate $\gamma\delta$ T-cells. In support of this position, enclosed herewith is a publication by Lang et al. (1995, *J. Immunol.* 154:5986-5994) which shows that phosphoantigens are known to activate $\gamma\delta$ T-cells and that activated $\gamma\delta$ T-cells are known to induce a IFN- γ production (see, e.g., abstract use of a phosphoantigen to reduce airway inflammation "would not work". In support of this conclusion, the Examiner cites Cendron et al. as describing phosphoantigens as being "mycobacterial non-peptide antigens" that require IL-2 to promote proliferation *in vitro* and *in vivo*, and that a strong initial Th1 response to phosphoantigens was seen in monkeys, but was followed by an anergic/hyporesponsive state where T cells are unresponsive to the antigen. The Examiner contends that the same response was shown in

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Sicard with another phosphoantigen, BrHPP. The Examiner contends that Sicard teaches that a transient $\gamma\delta$ T-cells response returns to baseline within 10-15 days and concludes that the prior art shows that $\gamma\delta$ T-cells do not exhibit sustained activation in response to phosphoantigens for any therapeutic benefit. Accordingly, the Examiner contends that it would require undue trial and error to practice the claimed invention.

The rejection of Claims 36-53 under 35 U.S.C. § 112, first paragraph, is respectfully traversed. The first paragraph of § 112 requires that a patent application be written so as to "enable any person skilled in the art to which it pertains . . . to make and use the same." A specification is presumed to be enabling absent "a reason to doubt the objective truth of the statements contained therein." *In re Marzocchi*, 169 USPQ 367, 369 (C.C.P.A. 1971). Further, a specification "may be enabling even though some experimentation is necessary," *United States v. Teletronics, Inc.*, 857 F.2d 778, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), so long as the amount of experimentation required is not "undue experimentation." *In re Wands*, 858 F. 2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The test is whether the specification "provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F. 2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Further, it is a tenet of patent law that an applicant need not teach what the skilled artisan already knows. Instead, it is preferred that an applicant "omit what is known in the art." *Hybritech Inc. v. Monoclonal Antibodies*, 231 USPQ 81, 94 (Fed. Cir. 1986). With this standard in mind, the rejection raised by the Examiner is discussed below.

Applicants submit that the Examiner is incorrect in making the statement that the claimed method "would not work". This is not at all supported by the specification, the knowledge in the art at the time of the invention, or the evidence of record. First, Applicants submit that it was known in the art at the time of the invention that phosphoantigens are a class of agents that can activate $\gamma\delta$ T-cells. In support of this position, enclosed herewith is a publication by Lang et al. (1995, *J. Immunol.* 154:5986-5994) which shows that phosphoantigens are known to activate $\gamma\delta$ T-cells and that activated $\gamma\delta$ T-cells are known to induce a IFN- γ production (see, *e.g.*, abstract and Introduction, where the phosphorylated molecules designated "TUBag" are phosphoantigens). Publications of Belmont et al. and Espinosa et al. (discussed below) are also enclosed herewith, and are additional evidence that it was known at the time of the invention that phosphoantigens could activate $\gamma\delta$ T-cells. The present inventors have demonstrated that activation of $\gamma\delta$ T-cells will inhibit airway hyperresponsiveness (AHR), and these publications show that phosphoantigens are one agent that will activate $\gamma\delta$ T-cells. Indeed, the Examiner also provides publications demonstrating that phosphoantigens will activate $\gamma\delta$ T-cells (see discussion below). Therefore, phosphoantigens are reasonably expected to be one agent with which the claimed method of the present invention can be performed.

With regard to the publications provided by the Examiner of Cendron et al. and Sicard et al., Applicants submit that these publications do not demonstrate, as the Examiner asserts, that the claimed invention "would not work". Each of Cendron et al.

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and Sicard et al. in fact demonstrate that phosphoantigens activate $\gamma\delta$ T-cells. Indeed, Sicard et al. conclude that administration of the phosphoantigen, BrHPP, represents a promising immunotherapeutic strategy for the induction of systemic Th1 cytokines and massive expansion of $\gamma\delta$ T-cells subset (see abstract, for example). Sicard et al. also note that their results only account for the "visible pool" of $\gamma\delta$ T-cells (in the periphery) and that the use of IL-2 may result in different means of activation/differentiation of $\gamma\delta$ T-cells than when they do not amplify (see page 5478, col. 2). It is clear that Sicard et al. do not conclude that the use of phosphoantigens to activate $\gamma\delta$ T-cells is ineffective and therefore, the Examiner's assertion to the contrary is not supported by the evidence of record. Cendron et al. also conclude that better recall responses to $\gamma\delta$ T-cells will be achieved, noting contrary results when the antigen is presented in a different form (see page 561, col. 2).

In addition, Applicants submit that for the purposes of controlling AHR, it is not necessary and in fact, not desirable, to have continuous, sustained activation of $\gamma\delta$ T-cells in response to phosphoantigens, nor continuous stimulation of Th1 type cytokines, and that a response that is transient or controllable is not a downside to use of phosphoantigens nor is it any indication that the claimed method would not work. The use of phosphoantigens in the claimed method is intended to prevent or reduce AHR when it occurs and it is not desirable to have a continuous $\gamma\delta$ T-cells activation. Indeed, it is generally not desirable to have continuous immune system activation when using an immunotherapeutic approach. The goals of the method can be met by a single stimulation of $\gamma\delta$ T-cells with a phosphoantigen to prevent or reduce AHR when it occurs, and so it is perfectly acceptable for the population of $\gamma\delta$ T-cells to increase for a period of days and then return to baseline.

Moreover, once activated, $\gamma\delta$ T-cells produce significant amounts of tumor necrosis factor- α (TNF- α), and exposure of $\gamma\delta$ T-cells to phosphoantigens increases the production of TNF- α by these cells. This is demonstrated by the attached publications, which describe the ability of activated $\gamma\delta$ T-cells to produce TNF- α , including in response to activation by phosphoantigens (Ismaili et al., 2002, *Clin. Immunol.* 103:296-302; and Wang et al., 2001, *J. Immunol.* 167:6195-6201). Referring to Ismaili, page 299-300, this publication teaches that $\gamma\delta$ T-cells produce TNF- α and that BrHPP (a known phosphoantigen) "further increased this basal production of TNF- α and also induced IFN- γ , secretion by $\gamma\delta$ T-cells ". Wang et al. teaches (see abstract) that human $\gamma\delta$ T-cells produce TNF- α as early as 2h after antigen exposure. Wang et al. also teach (page 6195, col. 1-2) that several "lines of evidence suggest that $\gamma\delta$ T-cells participate in the immune response to microbial pathogens by producing factors such as IFN- γ , and TNF- α ".

TNF- α , as acknowledged by the Examiner and as previously demonstrated by Applicants, inhibits airway hyperresponsiveness in sensitized and challenged mice, *via* an effect on the activity of $\gamma\delta$ T-cells. In addition, the inventors have demonstrated that administration of TNF- α reduces airway hyperresponsiveness independently of cellular inflammation in the lung. As evidence of this statement, Applicants enclose herewith a

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copy of a Declaration under 37 CFR § 1.132 that was submitted by the inventors and is of record in the parent application (U.S. Patent Application No. 09/672,865). Accordingly, Applicants have shown that activation of $\gamma\delta$ T-cells can inhibit airway hyperresponsiveness (AHR), and Applicants have also previously demonstrated one such agent for activation of $\gamma\delta$ T-cells which results in the inhibition of AHR is TNF- α . Applicants further demonstrate herein that phosphoantigens can also activate $\gamma\delta$ T-cells (see above), which accordingly will be expected to inhibit AHR according to the invention. Furthermore, Applicants provide evidence herein that one result of such activation of $\gamma\delta$ T-cells by phosphoantigens is the further induction of TNF- α (see above), which as discussed has already been shown by the inventors to have a corresponding effect on $\gamma\delta$ T-cells and AHR. Taken together, this evidence demonstrates that phosphoantigens administered in the presently claimed method are reasonably expected to inhibit AHR, and that the claimed invention is fully enabled."

It remains the Examiner's position that those skilled in the art could not extrapolate the disclosure of the specification into a method to reduce airway hyperresponsiveness in a mammal by administering a phosphoantigen. The declaration submitted in application 09/672, 865 on 10/14/2003 in particular is insufficient to overcome this rejection because the declaration addresses the administration of TNF- α , not phosphoantigen. Further, the administration of TNF- α has already been indicated by the Examiner to be enabled. Therefore, the declaration is not persuasive in the instant rejection which is directed to phosphoantigens. The references submitted on 09/04/2007 also do not provide support for a method for reducing airway hyperresponsiveness in a mammal by administering any phosphoantigen. Neither the specification, nor the state of the art at the time of invention provides adequate support to enable the instant claims. Therefore, those skilled in the art at the time of the invention would not know to use IPP or any phosphoantigen in general to perform the recited method.

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6. Claims 36-53 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of : a method to reduce airway hyperresponsiveness in a mammal, consisting essentially of increasing gamma delta T cell action in a mammal that has, or is at risk of developing, a respiratory condition associated with airway hyperresponsiveness by administering TNF-alpha to the lung tissue of said mammal wherein administration of said TNF-alpha reduces airway hyperresponsiveness in said mammal; wherein said TNF-alpha is administered so that gamma delta T cells in the lung tissue of said mammal increases; wherein said TNF-alpha is administered so that gamma delta T cells in said mammal are activated; wherein said TNF-alpha is targeted to gamma delta T cells in the lung tissue of said mammal; wherein said TNF-alpha is targeted to gamma delta T cells having T cell receptor selected from the group consisting of a murine TCR comprising Vgamma4 and a human TCR comprising Vgamma1; wherein said TNF-alpha is administered by a route selected from the group consisting of inhaled, intratracheal and nasal routes; wherein said TNF-alpha is administered to said mammal in an amount effective to reduce airway hyperresponsiveness in said mammal as compared to prior to administration of said TNF-alpha; wherein said TNF-alpha is administered with a pharmaceutically acceptable excipient; wherein said TNF-alpha is administered within between 1 hour and 6 days of an initial diagnosis of airway hyperresponsiveness in said mammal; wherein said TNF-alpha is administered within less than about 72 hours of an initial

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diagnosis of airway hyperresponsiveness in said mammal; wherein said TNF-alpha is administered prior to development of airway hyperresponsiveness in said mammal; wherein increasing gamma delta T cell action by administration of said TNF-alpha decreases airway methacholine responsiveness in said mammal; wherein increasing gamma delta T cell action by administration of said TNF-alpha reduces airway hyperresponsiveness of said mammal such that the FEV1 value of said mammal is improved by at least about 5%; wherein increasing gamma delta T cell action by administration of said TNF-alpha improves said mammal's PC_{20methacholine} FEVt value obtained before increasing gamma delta T cell action when the mammal is provoked with a first concentration of methacholine is substantially the same as the PC_{20methacholine} FEVt value obtained after increasing gamma delta T cell action when the mammal is provoked with double the amount of the first concentration of methacholine; wherein said first concentration of methacholine is between about 0.01 mg/ml and about 8 mg/ml; wherein said airway hyperresponsiveness is associated with a disease selected from the group consisting of chronic obstructive disease of the airways and asthma.

Applicant is not in possession of : a method to reduce airway hyperresponsiveness in a mammal, comprising increasing gamma delta T cell action in a mammal that has, or is at risk of developing, a respiratory condition associated with airway hyperresponsiveness by administering **a phosphoantigen** to said mammal, wherein administration of said **phosphoantigen** reduces airway hyperresponsiveness in said mammal of claim 36; wherein the **phosphoantigen** comprises **isoprenylpyrophosphate (IPP)** of claim 37; wherein said **pyrophosphate** is administered so that gamma delta T cells in the lung tissue of said mammal increases of claim

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38; wherein said **phosphoantigen** is administered so that gamma delta T cells in said mammal are activated of claim 39; wherein said **phosphoantigen** is targeted to gamma delta T cells in the lung tissue of said mammal of claim 40; wherein said **phosphoantigen** is targeted to gamma delta T cells having T cell receptor selected from the group consisting of a murine TCR comprising Vgamma4 and a human TCR comprising Vgamma1 of claim 41; wherein said **phosphoantigen** is administered by a route selected from the group consisting of inhaled, intratracheal and nasal routes of claim 42; wherein said **phosphoantigen** is administered to said mammal in an amount effecting to reduce airway hyperresponsiveness in said mammal as compared to prior to administration of said phosphoantigen of claim 43; wherein said **phosphoantigen** is administered with a pharmaceutically acceptable excipient of claim 44; wherein said **phosphoantigen** is administered within between 1 hour and 6 days of an initial diagnosis of airway hyperresponsiveness in said mammal of claim 45; wherein said **phosphoantigen** is administered within less than about 72 hours of an initial diagnosis of airway hyperresponsiveness in said mammal of claim 46; wherein said **phosphoantigen** is administered prior to development of airway hyperresponsiveness in said mammal; wherein increasing gamma delta T cell action by administration of said **phosphoantigen** decreases airway methacholine responsiveness in said mammal of claim 48; wherein increasing gamma delta T cell action by administration of said **phosphoantigen** reduces airway hyperresponsiveness of said mammal such that the FEV1 value of said mammal is improved by at least about 5% of claim 49; wherein increasing gamma delta T cell action by administration of said **phosphoantigen** improves said mammal's PC_{20methacholine} FEVt value obtained before increasing gamma delta T cell action when the mammal is provoked with a first concentration of methacholine is substantially the same as

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the PC_{20methacholine} FEVt value obtained after increasing gamma delta T cell action when the mammal is provoked with double the amount of the first concentration of methacholine of claim 50; wherein said first concentration of methacholine is between about 0.01 mg/ml and about 8 mg/ml; wherein said airway hyperresponsiveness is associated with a disease selected from the group consisting of chronic obstructive disease of the airways and asthma for the same reasons as set forth in the Office Action mailed on 05/03/2007.

Applicant's arguments filed on 09/04/2007 have been fully considered, but are not found persuasive.

Applicant argues that the specification teaches that:

"For the activation of $\gamma\delta$ T cells, the present invention also includes the use of 'phospho-antigens'. Phospho-antigens are antigens containing phosphate groups such as isoprenylpyrophosphate (IPP) and many others that have been characterized by the research groups of Michael Brenner and others (e.g., Tanaka et al., 1995, *Nature* 375:155-158)" (Page 31, lines 21-24). Therefore, the specification clearly teaches the use of phosphoantigens (spelled "phospho-antigen" in the specification, which is simply an alternate spelling for the term, as discussed above) for use in activation of $\gamma\delta$ T cells, and provides a reference to the knowledge of such phosphoantigens in the art. To attempt to obviate the Examiner's concerns, as discussed above, the specification has been amended to remove the hyphen in the word "phosphoantigen" so that it is more consistent with the spelling used in the literature. Given that the specification provides a definition and reference to a publication clearly establishing the identity of the term, this amendment adds no new matter.

Moreover, the term "phosphoantigens" was well-known to those of skill in the art at the time of the invention. As evidence of this position, enclosed herewith are two publications (Belmant et al., 2000, *FASEB* 17:1669-1670; and Espinosa et al., 2001, *Microbes and Infection* 3:645-654), both of which establish that the term "phosphoantigen" was well-known in the art at the time of the invention, and that multiple examples of natural and synthetic phosphoantigens were known. These references also further establish that at the time of the invention, it was known that phosphoantigens could activate $\gamma\delta$ T cells. Accordingly, the art already recognizes the structural features common to the genus of phosphoantigens and therefore, the skilled

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artisan does not need to "figure out what a phosphoantigen looks like". One of skill in the art is already apprised of what is a phosphoantigen, including different examples of members of the genus, and accordingly, one of skill in the art can readily envision multiple contemplated phosphoantigen possibilities recited in the instant claims. Establishment of sufficient written description does not require that Applicants describe each and every embodiment that may fall within the scope of the claims. The analysis of whether the specification complies with the written description requirement should be conducted from the standpoint of one of skill in the art at the time the application was filed (see, e.g., *Wang Labs. v. Toshiba Corp.*, 993 F.2d 858, 865, 26 USPQ2d 1767, 1774 (Fed. Cir. 1993)) and should include a determination of the field of the invention and the level of skill and knowledge in the art. Information which is well known in the art need not be described in detail in the specification. See, e.g., *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379-80, 231 USPQ 81, 90 (Fed. Cir. 1986) (emphasis added). See also MPEP 2163II(A)(2). Applicants submit that the specification description is sufficient to place the inventors in possession of the claimed invention at the time of filing.

With regard to the Examiner's concern that throughout the literature "IPP" stands for a different molecule, namely isopentenylpyrophosphate, it is agreed that in the literature, isopentenylpyrophosphate is also denoted by the acronym, IPP. However, it is noted that isopentenylpyrophosphate is in fact a particular compound included in the larger family of isoprenylpyrophosphates. "Isoprenyl" is a more generic term than "isopentenyl", and in fact "prenyl" stands for a skeleton of 5n carbon atoms; however, this carbon skeleton can undergo various substitutions resulting in many different products (alcohol moiety, acid moiety, different alkyl substitutions, etc...). When n=1, then isoprenyl is isopentenyl (C5, n=1), but larger isoprenyls exist (e.g., geranyl (C10, n=2), farnesyl (C15, n=3), geranylgeranyl (C20, n=4)). Therefore, one isoprenylpyrophosphate that can be used in the present invention would be isopentenylpyrophosphate. "

It is the Examiner's position that the specification has not adequately described a correlation between function (reduces airway hyperresponsiveness) and structure responsible for reducing airway hyperresponsiveness such that one of ordinary skill in the art would have known which phosphoantigens could be used to generate the disclosed function of reducing airway hyperresponsiveness in a mammal. Possession may not be shown by merely describing how to obtain possession of members of the claimed genus or how to identify their common structural

features. See University of Rochester, 358 F.3d at 927, 69 USPQ2d at 1895. "Without a correlation between structure and function, the claims do little more than define the claimed invention by function. That is not sufficient to satisfy the written description requirement." Ex parte Kubin, 83 U.S.P.Q.2d 1410 (BPAI 2007). The specification does not adequately describe the genus of all phosphoantigen non-peptide compounds for use in the claimed invention.

Contrary to Applicant's assertion one of ordinary skill in the art would not be able to determine which phosphoantigens would work in the claimed invention since neither the exemplary embodiments nor the specification's general method appears to describe structural features, in structural terms, that are common to the genus of phosphoantigens that would work to reduce airway hyperresponsiveness in the claimed invention. Applicant's assertion that all phosphoantigens would work is not supported by examples or description in the specification. Further, the art shows that "both the number and position of the phosphate groups, as well as the residues connected with the carbon backbone are required for stimulation" of $\gamma\delta$ T cells. (In particular, Burk et al., PTO-892, Reference U, abstract, whole document). No such structure requisite structure has been described in the specification.

7. No claim is allowed.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nora M. Rooney whose telephone number is (571) 272-9937. The examiner can normally be reached Monday through Friday from 8:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

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Nora M. Rooney, M.S., J.D.

Patent Examiner

Technology Center 1600

Ma her m. Haddad
MAHER M. HADDAD
PRIMARY EXAMINER